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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/300,959	04/27/1999	MAURIZIO ZANETTI	P-ZA-3519	5037

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/300,959	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/3/03 has been entered. As requested the response filed on 7/29/03, previously non-entered as indicated in the advisory action mailed on 10/27/03, has been entered. Claims 1-29, and 31-37 have been canceled and new claims 38-68 have been entered. Claims 38-68 are currently pending and under examination at this time. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Priority

New claims 38, and 41-44 are entitled to benefit of priority to the filing date of the parent application, April 27, 1998. New claims 39-40, 43, and 45-68 are only entitled to the benefit of priority to the filing date of the instant application, April 27, 1999.

The applicant is reminded that the previous office actions, see in particular the office

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action mailed on 7/21/01, clearly indicated that the parent application 60/083,154 does not

disclose the following subject matter: nucleic acids encoding a polypeptide fused with a cytokine, or the targeting of a nucleic acid to hematopoietic cells *ex vivo* as part of a method for treating a condition. Thus, the aforementioned subject matter is not granted the priority date of the parent application, and is only entitled to benefit of priority to the filing date of the instant application, April 27, 1999. Therefore, new claims 39-40, 43, and 45-68, which recite the aforementioned subject matter, are only entitled to benefit of priority to April 27, 1999.

Claim Rejections - 35 USC § 112

The rejection of canceled claims 3-4, 18-21, 29, 31-32, and 34-37 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained in part over new claims 38, 41, and 42. Applicant's arguments and the declarations under 37 C.F.R. 1.132 by Maurizio Zanetti have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

The previous office action identified the following enabled subject matter: methods of stimulating an immune response and methods of treating a condition in a mammal comprising the intrasplenic injection of a DNA plasmid comprising a nucleic acid encoding a heterologous polypeptide antigen operably linked to a B cell expression element, wherein the expression of said heterologous polypeptide antigen in B cells results in the stimulation of an immune response against said antigen.

Please note that the applicant has overcome the previous grounds of rejection concerning the use of recombinant nucleic acids other than plasmid DNA by amending the claims to recite a plasmid vector.

In regards to routes of immunization other than intrasplenic injection and the unpredictability of targeting B cells in vivo, the applicant argues that the specification identifies other target tissues, such as lymph nodes. However, as previously noted, the cellular composition of the spleen versus gut associated lymph organs, or lymph nodes is very different in terms of the percentages of different antigen presenting cells and the types of antigen presenting cells present. Although the specification and previously provided declaratory data, exhibit B, demonstrates that direct injection of the spleen results in the generation of immune responses, the specification fails to provide any evidence that the administration of plasmid vectors to any other lymphoid tissue would result in comparable levels of antibody or T cell mediated responses. In the instant declaration by Maurizio Zanetti, Dr. Zanetti states that there are high percentages of B cells in lymphoid tissues other than spleen. However, it is clear from the percentages provided by Dr. Zanetti that lymph nodes on contain about half the number of B cells as the spleen, and that peripheral blood contains even less. Thus, while the office acknowledges the comments made in the declaration by Maurizio Zanetti, that lymph tissue other than the spleen contains B cells, the declaration fails to provide concrete evidence that the level of B cells in the spleen versus peripheral lymph nodes is equivalent or that B cells present in a peripheral lymph node are capable of stimulating therapeutic immune responses following direct injection of a plasmid or other nucleic acid to the lymph node. Furthermore, in regards to the post-filing publication provided as exhibit 2 in the declaration, the article by Maloy et al. is not equivalent to the methods of immunization disclosed and claimed by the applicants. While the Maloy et al. reference discloses direct intranodal administration of plasmid DNA encoding an antigen resulting in antigen specific immune responses, the plasmid DNA taught by Maloy et al. does not

utilize a B cell specific promoter. Further, Maloy et al. clearly demonstrates that the cells which express the naked DNA vaccine in their experiments are dendritic cells, not B cells (Maloy et al., page 3302-3303, bridging paragraph). Thus, a nexus cannot be made between the results achieved by Maloy et al. where dendritic cells are transfected following intranodal vaccination and applicants methods which depend on B cell specific expression of the antigen following intranodal injection of the plasmid vector.

In addition, please note that while claim 38 is limited to the administration of the plasmid vector to lymphoid tissue, claims 41-42 are not so limited and broadly read on the administration of the plasmid vector by any route of administration. The applicant's instant arguments are directed to the administration to lymphoid tissue and do not address the lack of enablement for administration to non-lymphoid tissue. The previous office actions have stated that the specification fails to provide an enabling disclosure for targeting B cells using any route of administration. Further, the articles cited in the previous office actions, particularly Deonarian and Miller, clearly teach that specific targeting of a nucleic acid to a particular cell was unpredictable at the time of filing. For example, Deonarain teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al., page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al., page 198,

paragraph 2). The specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to B cells *in vivo*. Therefore, in view of the art recognized unpredictability of targeted gene expression *in vivo*, the lack of guidance provided by the specification for plasmid vectors suitable for specifically targeting B cells, the lack of working examples concerning methods of targeted delivery other than intrasplenic injection, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 19-20 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of the cancellation of these claims.

Claims 38-43, and 58-68 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention.

Claim 38-43 appear to lack a method step which results in the recited use of the method in the preamble. Claims 38-41 are directed to methods for stimulating an immune response and claims 42-43 are directed to methods of treating a condition; however, the steps recited only appear to result in the expression of the heterologous epitopes in the B cell. The claims as written lack a step or limitation relating the expression of the heterologous epitope to the stimulation of an immune response or the treatment of a condition. As such, the claims are incomplete. The following amendments are suggested to overcome this rejection. For claims 38-41, it is suggested that the applicant amend the claims to add the phrase, " wherein the expression of said one or more heterologous epitopes in said B cell results in the stimulation of an immune response". For claims 42-43, it is suggested that the applicant amend the claims to add the phrase, "wherein the expression of said heterologous epitope in said B cell results in the stimulation of an immune response which treats a condition".

Claim 39 is indefinite in that the claim recites the administration of a plasmid vector to a lymphoid tissue *ex vivo* in order to stimulate an immune response. The claim is confusing as the methods steps do not include the administration of either the plasmid vector or B cells or lymphoid tissue to a mammal such that an immune response could be generated. It is therefore unclear whether the applicant is claiming an *in vivo* method of stimulating an immune response or an *in vitro* method of expressing a heterologous epitope in lymphoid tissue *ex vivo*.

Claim 58 recites the plasmid vector of claim 55 and add the limitation wherein the cytokine is selected from a group of cytokines. However, claim 55 already limits the cytokine to interleukin-12. The limitations of claims 58 and 55 are in conflict. Thus, the metes and bounds of the claims cannot be determined as it is unclear whether the applicant intends to claim a second cytokine selected from the listed group. Claims 59-68 depend on claim 58 and further recite specific cytokines including interleukin-12. As noted for claim 58, the limitations of claims 59-68 are in conflict with the limitation of claim 55 which already identifies the cytokine as interleukin-12. In regards to claim 67, please note that this claim also appears to be improper as it fails to further limit claim 55 since both claim recite wherein the cytokine is interleukin-12.

Claim Rejections - 35 USC § 103

The rejection of claims 3-4, 29, 31, and 35 under 35 U.S.C. 103 over Hurpin et al. in view of Banerji et al. is withdrawn in view of the cancellation of these claims. Please note that new claims 44-68 are newly rejected under 35 U.S.C. 103(a) below.

Claims 40, 43, and 45-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,891,432 (1999), hereafter referred to as Hoo, in view of Banerji et al. (1983) Cell, Vol. 33, 729-740. The applicant claims plasmids vectors comprising a gene encoding a fusion polypeptide comprising an antigen fused to a cytokine operatively linked to a B cell expression element. The applicant further claims said plasmid vectors wherein the cytokine is one of interleukins 2, 4, 5-7, 10, 12, or 15, interferon-gamma, or GM-CSF. In addition, the

applicant claims methods of stimulating an immune response or treating a condition by transfecting B cells *ex vivo* with a plasmid vector encoding a heterologous antigen under transcriptional control of a B cell expression element and administering the cells to an individual.

Hoo et al. teaches recombinant nucleic acids encoding an antigen fused to a membrane bound cytokine, where the cytokine is selected from a group which includes interleukins 2, 4, 5-7, 10, 12, or 15, interferon-gamma, or GM-CSF, and the expression of the encoded fusion proteins in cells using plasmid vectors (Hoo et al., columns 1, 3, 5, 12, Table 1, and column 18). Hoo et al. further teaches methods of stimulating an immune response and methods of treating disease by administering to an individual a cell comprising an antigen fused to a membrane-bound cytokine, wherein the cell is a myeloma or plasmacytoma (Hoo et al., columns 19-22, and columns 49-50, claims 13-24). Please note that myeloma and plasmacytomas are transformed B cells.

Hoo et al. differs from the instant invention as claimed by failing to particularly teach that B cell expression elements are included in the plasmid vectors to express the fusion proteins. Hoo et al. generally teaches that the genes encoding the fusion proteins are operatively linked to promoters and gives the SV40 promoter as an example. Banerji et al. supplements Hoo by teaching a plasmid encoding the b-globin gene operatively linked to the immunoglobulin enhancer which is a B cell specific expression element (Banerji et al., page 730, Figure 1, and page 732, Figure 2). Banerji et al. further provides motivation for using a B cell specific expression elements in myeloma cells by teaching that use of the immunoglobulin heavy chain enhancer to express a heterologous gene, b-globin, in myeloma cells results in two fold increase

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in the magnitude of b-globin expression compared to vectors which utilize the viral SV40

enhancer (Banerji et al., page 729, abstract, and page 731, column 2, paragraph 3). Thus, based on the increased magnitude of gene expression using the immunoglobulin promoter in myeloma cells versus a viral promoter such as SV40 as taught by Banerji et al., it would have been *prima facie* obvious at the time of filing to substitute the immunoglobulin heavy chain transcriptional elements taught by Banerji et al. for the viral elements taught by Hoo in order to increase antigen expression in B cells such as myeloma cells or plasmacytomas. Based on the activity of the immunoglobulin promoter observed by Banerji in myeloma cells and the high degree of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in modifying the plasmid vectors taught by Hoo to include the immunoglobulin promoter and enhancer and using said vectors according to the methods taught by Hoo to generate immune responses.

Applicant's arguments regarding the teachings of Banerji et al. as they apply to the instant rejection have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims. The applicant argues that there is no motivation to substitute the immunoglobulin enhancer for a viral enhancer since the applicant states that Banerji et al. teaches that the immunoglobulin enhancer behaves similarly to the SV40 enhancer. However, on page 731, column 2, paragraph 3, Banerji et al. clearly states that the Ig enhancer is more effective in myeloma cells than the SV40 enhancer. In addition, even if applicant's interpretation of the teachings of Banerji et al. were accepted, motivation for substituting the Ig expression elements for SV40 would still be present since Hoo teaches that many promoters can be used, and since the Ig promoter and enhancer are at least as effective as the SV40 enhancer

recited in Hoo, the skilled artisan would have been equally motivated to use either promoter to express the fusion proteins disclosed by Hoo with a reasonable expectation of success.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER